REMARKS

Claims 27 and 38-85 were pending in the instant application. Claims 27, 51, 56-60, 75-80, 84, and 85 have been amended, and new claim 86 has been added. Support for the amendments to the claims and the new claim can be found in the specification and claims, as originally filed. Specifically, support for the amendment to claim 51 can be found in claim 48, as filed. Support for the amendments to claims 56-59 and 75-78 can be found at least at page 4, line 17 through page 5, line 4, Example 2, page 8, and page 21. Support for the amendments to claims 27, 60, 79, 80, 84, and 85 can be found at least at page 1, lines 13-14, page 2, lines 12-13, page 40, lines 5-22, Example 2, Figures 1 and 2, and page 42, lines 19-22. Support for new claim 86 can be found in claim 27, as filed, and at least at page 1, lines 13-14, page 2, lines 12-13, page 40, lines 5-22, Example 2, and Figures 1 and 2. Upon entry of the present Amendment, claims 27 and 38-85 are pending and presented for reconsideration. Applicants respectfully submit that no new matter is introduced by the present Amendment.

In a Response to Restriction Requirement earlier filed on March 22, 2006, Applicants elected Group I, drawn to claims 27, 38-59, 79, and 81, without traverse. Applicants further elected the species of Type II diabetes, for search purposes only. It is the Applicants' understanding that under 35 U.S.C. §121, an election of a single species for prosecution on the merits is required, to which the claims will be restricted if no generic claim is finally held allowable. Applicants further understand that upon the allowance of a generic claim, they will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R.§1.141 *et seq.*

Amendment and/or cancellation of the claims is not to be construed as acquiescence to any of the objections/rejections set forth in the instant Office Action or any previous Office Action of the parent application, and was done solely to expedite prosecution of the application. Applicants submit that claims were not added or amended during the prosecution of the instant application for reasons related to patentability. Applicants reserve the right to pursue the claims, as originally filed, or similar claims in this or one or more subsequent patent applications.

Acknowledgment of the Examiner's Withdrawal of Certain Rejections

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection of claims 52-55 under 35 U.S.C. 112, second paragraph, the rejection of claims 38-42 and 45 under 35 U.S.C. 102(a) as being anticipated by Jiang *et al.*, and the rejection of claims 27, 38-59 and 81-85 under 35 U.S.C. 112, first paragraph, as set forth in the Office Action dated February 22, 2007.

Advisory Action Dated August 7, 2007

In the Advisory Action dated August 7, 2007, the Examiner indicated that the Amendment and Response filed on July 25, 2007 will be partially entered and that the affidavit or other evidence filed on July 25, 2007 will not be entered. Therefore, in order to procedurally ensure that all of the amendments, evidence, and Declaration of the inventors under 37 CFR §1.132 are fully considered and entered, Applicants provide herein further claim amendments and explanations and also reiterate herein the arguments provided in the July 25, 2007 Amendment and Response.

Rejection of claims 27, 38-59, 79, and 8-85 under 35 U.S.C. § 112, First Paragraph

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection of claims 27, 38-59, 79, and 81-85 under 35 U.S.C. §112, first paragraph in the Advisory Action dated August 7, 2007. However, in order that these amendments are fully considered and entered, Applicants reiterate herein the response provided in the July 25, 2007 Amendment and Response to Final Office Action.

In the Final Office Action dated February 22, 2007, claims 27, 38-59, 79, and 81-85 were rejected under 35 U.S.C. §112, first paragraph, because allegedly the specification, while being enabling for the methods *in vitro*, does not reasonably provide enablement for such methods performed *in vivo* . In particular, the Office Action states, on page 4, that "[t]his rejection could be overcome by requiring that the recited adipocytes must be 'isolated'."

Without acquiescing to this rejection and solely in an effort to further prosecution, Applicants amended claims 27, 38-59, 79, and 81-85 to refer to "contacting a culture of ***isolated*** adipocytes with siRNA." Applicants, therefore, respectfully request that the Examiner's withdrawal of the rejection of claims 27, 38-59, 79, and 81-85 under 35 U.S.C. §112, first paragraph in the Advisory Action dated August 7, 2007 be entered.

Claim Rejections - 35 U.S.C. §103

Rejection of claims 27, 44-48, 50, 51, 56-59, 79, and 81-83 under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 27, 44-48, 50, 51, 56-59, 79, and 81-83 as being unpatentable over Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) in view of Clancy *et al.* (US 20030087259). The Examiner states on pages 4-5 of the Office Action that, "Al-Hasani taught methods of studying genes related to glucose transport. Specifically, Al-Hasani investigated the relationship between the GTPase dynamin and endocytosis of the GLUT4 glucose transporter in cultured rat adipocytes." The Examiner admits that, "Al-Hasani did not teach the use of siRNA." The Examiner then states that "Clancy taught that the activity of a polypeptide in a cell can be controlled by several alternative means including the use of negative mutants of the protein and the use of antisense or siRNA directed at the mRNA encoding the protein." In conclusion, the Office Action states, on page 5, that, "it would have been obvious to one of ordinary skill in the art at the time of the invention to use siRNA directed against dynamin to assess its role in the endocytosis of GLUT4."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)).

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness since the skilled artisan would have found neither a reasonable expectation of success nor the motivation to arrive at the claimed invention given the teachings of the cited references.

The claims, as amended herein, are directed to a method of identifying a gene that affects glucose transport, or a method of identifying a gene involved in an insulin response disease or disorder, the methods comprising: (a) contacting ***a culture of isolated adipocytes*** with siRNA targeted against the gene, thereby forming a mixture; (b) electroporating the mixture ***under conditions such that the siRNA is introduced into the adipocytes at an efficiency such that expression of the targeted gene is reduced by at least 70% in the culture of adipocytes when maintained under conditions suitable for the siRNA to mediate RNAi of the targeted gene***; and (c) assaying glucose transport in the adipocytes, wherein a modulation in glucose transport indicates that the targeted gene affects glucose transport; thereby identifying a gene that affects glucose transport or a gene that is involved in an insulin response disease or disorder.

The claims have been amended to recite an essential feature of the instant invention which distinguishes the claimed invention over the cited art. As taught in the instant specification and described in detail in the arguments presented herein, in order to effectively identify target genes that affect glucose transport in adipocytes, ***it is essential that the adipocyte population exhibit sufficient reduction in expression of the targeted gene to be able to reliably assay that gene's effect on glucose transport***. The instant inventors achieved such an effect by developing a highly efficient methodology of introducing nucleic acid molecules which interfere with expression of the targeted gene, *i.e.*, siRNAs mediating RNA intererference of the targeted gene. The methodology efficiently introduces the siRNA into ***virtually all of the adipocytes in the population*** with little to no adverse toxicity effects. Moreover, the siRNAs are highly effective at reducing expression of the target gene after sufficient culturing of the population. Thus, the methodology provides for highly efficient introduction of the siRNAs such that gene reduction occurs at a level suitable to assay the gene's effect on the glucose transport activity of the adipocyte population. Such a methodology is nowhere taught or suggested by the prior art.

Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) describe the characterization of the mechanism of GLUT4 endocytosis by overexpressing a dominant-negative mutant of dynamin-1 in rat adipose cells (see page 17504, column 2, lines 46-48 of Al-

Hasani *et al.*). In order to study the role of dynamin in GLUT4 endocytosis, Al-Hasani *et al.* overexpress a plasmid encoding a dominant-negative mutant of dynamin-1 in isolated rat adipose cells. The effects of dynamin-1 on GLUT4 trafficking are monitored using a co-transfected recombinant GLUT4 containing a hemaglutinin (HA) tag. The methodology of Al-Hasani is designed to transfect adipose cells with ***DNA and DNA expression plasmids*** (see, *e.g.*, page 17505, column 1, second paragraph of Al-Hasani *et al.*). In particular, the methods involve transfection of cells with large amounts of ***plasmid DNA*** (*e.g.*, 5 μg plasmid DNA per transfection). Large amounts of carrier DNA are utilized (*e.g.*, 100μg carrier DNA). Pulse conditions are specified for the described ***plasmid DNA*** transfection. The reference is silent as to capacitance. Specifically, Al-Hasani *et al.* disclose that "***only 10% of the cells are transfected***" (see, *e.g.*, page 17505, right column, second paragraph of Al-Hasani *et al.*) (Emphasis added). It would not have been obvious, based on the teachings of Al-Hasani *et al.* regarding the low efficiency of DNA transfection into adipocytes that ***successful electroporation of an adipocyte population with siRNA such that gene reduction would occur at a level suitable to assay the gene's effect on the glucose transport activity of the adipocyte population could be accomplished***, as required by the currently pending claims.

Clancy *et al.* (US 20030087259) fail to remedy the deficiencies of Al-Hasani *et al.* Clancy *et al.* simply teach diagnostic assays for detecting bone and cartilage formation and therapeutic methods for treating disease and disorders related to bone and cartilage formation or resorption. Clancy *et al.* teach siRNAs as a component of a composition comprising "a plurality of antagonists of a plurality of genes" (see *e.g.*, para. [0009]). Clancy *et al.* also teach siRNAs as potential agents for "blocking or reducing the expression of a gene or the activity or level of the encoded polypeptide that is modulated, *e.g.*, upregulated, during normal bone or cartilage formation" (see *e.g.*, para. 0239)). There is no teaching or suggestion in Clancy *et al.* regarding the successful electroporation of an adipocyte population with siRNA such that gene reduction would occur at a level suitable to assay the gene's effect on the glucose transport activity of the entire adipocyte population.

In the Advisory Action mailed on August 7, 2007, the Examiner alleges that

> [t]he activity of siRNA in one cell has nothing to do with protein expression in another cell, such that if one cell takes up siRNA, one can reasonably expect to obtain inhibition of gene expression in that cell regardless of whether or not other cells in the culture

> were transfected. Applicant may have meant to argue that transfection of only 10% of the cells in a culture would be insufficient for the purposes of studying glucose transport. This would be unpersuasive because 10% efficiency proved to be efficient for Al-Hasani.

Applicants wish to emphasize again that the essential feature of the invention that distinguishes the claimed invention over the cited art is that, in order to effectively identify target genes effecting glucose transport in adipocytes, it is essential that the ***adipocyte population exhibit sufficient reduction in expression of the targeted gene*** in order to be able to reliably assay that gene's effect on glucose transport. The instant inventors achieved such an effect by developing a highly efficient methodology of introducing nucleic acid molecules which interfere with expression of the targeted gene, *i.e.*, siRNAs mediating RNA intererference of the targeted gene. The methodology efficiently introduces the siRNA into ***virtually all of the adipocytes in the population*** with little to no adverse toxicity effects. Moreover, the claimed siRNAs are highly effective at reducing expression of the target gene after sufficient culturing of the population.

It was well known in the art at the time of filing that electroporation of DNA into adipocytes only leads to the successful expression of DNA in only a small minority of the adipocyte population (***approximately 1-10%***[1]). In contrast, in order for siRNA to successfully silence the gene of interest, *i.e.*, mediate RNA interference, in the population of adipocytes, as currently claimed, it is required that virtually all of the cultured adipocytes (***approximately 100%***) take up functional siRNA. ***Since the successful electroporation of DNA into a population of adipocytes is typically less than 10% efficient, it would <u>not</u> have been obvious to one of ordinary skill in the art at the time of filing of the instant invention that electroporation of siRNA into a culture of isolated adipocytes would be nearly 100% efficient***[2] and that ***the adipocyte population would exhibit sufficient reduction in expression of the targeted gene.*** A skilled artisan would have had an appreciation of these significant differences and would <u>not</u> have reasonably expected that mere substitution of the siRNAs of Clancy *et al.* for the plasmid DNAs transfected in Al-Hasani *et al.* would be successful. Additionally, the declaration of the inventors under 37 CFR §1.132, attached herein as Appendix A, further indicates that, prior to

[1] See, *e.g.*, page 40, lines 15-17 of the instant specification and page 17505, right column, second paragraph of Al-Hasani *et al.*
[2] Using labeled siRNA, Figure 1B, left panels, and Example 2, page 40, lines 1-17, of the specification demonstrate that the electroporation of siRNA into adipocytes was, unexpectedly, nearly 100% efficient.

Applicants' demonstration that such electroporation of siRNA into a culture of isolated adipocytes was possible according to the claimed methods of this invention, there was no reasonable expectation that such successful electroporation and sufficient reduction in expression of the targeted gene could be accomplished.

The art is also replete with teachings which support the non-obviousness of the present invention. Following are several examples demonstrating the difficulty of transfecting adipocytes with siRNA and the successful use of the present invention to electroporate adipocytes with siRNA:

(a) As demonstrated in Appendix B, in 2006 Robinson *et al.* state that "adipocytes are difficult to transfect, and until recently, successful siRNA transfection was achieved only via electroporation" (see, *e.g.*, page E885, second column, third full paragraph). Robinson *et al.* go on to cite a 2004 scientific publication of one of the inventors of the instant application, M. Czech, as the group which was successful in transfecting adipocytes with siRNA using electroporation.

(b) As demonstrated in Appendix C, the 2006 Panomics DeliverX Plus siRNA Transfection Kit Brochure discloses that "[t]ransfection of siRNA into differentiated 3T3-L1 adipocytes... has only been accomplished by electroporation" (see, *e.g.*, first page, left column) and specifically references the 2003 *Proceedings of the National Academy of Sciences* scientific publication by the instant inventors which corresponds to the instant patent application. This Brochure goes on to further disclose that "***adipocytes... represent one of the most difficult-to-transfect cell lines used routinely in cell biology studies***" (see, *e.g.*, page 2, right column, second full paragraph) (Emphasis added).

(c) As demonstrated in Appendix D, Jain discloses that "***adipocytes are fully differentiated cells with no proliferation and are thus difficult to transfect*** by either RNAi or ASO approaches" (see, *e.g.*, page 308, middle column, first paragraph) (Emphasis added).

(d) As demonstrated in Appendix E, Venugopal *et al.* disclose that "***adipocytes... proved difficult to transfect efficiently with siRNA***" (see, *e.g.*, page 17122, second column, first full paragraph) (Emphasis added).

Applicants also describe in their specification the problems existing in the art at the time of the invention. In particular, Applicants teach in the specification on page 1, lines 23-24 that

adipocyte "cells are difficult to work with and are not easily transfected with reagents that work in other cells such as fibroblasts." Furthermore, it was well known in the art at the time of the invention that the transfection of a culture of cells with DNA differs dramatically from the transfection of a culture of cells with siRNA, and that the transfection of siRNA varies greatly based on cell-type. For example, Walters and Jelinek[3] teach that the effectiveness of siRNAs may depend on the method of transfection (see title and abstract of Walters and Jelinek (2002) *Antisense and Nucleic Acid Drug Development* 12:411-418). More specifically, Walters and Jelinek teach the "striking dependence of dsRNA-mediated gene silencing in some cells on the methods of dsRNA transfection"(see Abstract of Walters and Jelinek). Additionally, Weil *et al.*[4] also teach that "the first difficulty with implementing RNA interference in a new cell type is optimizing the transfection procedure" (see page 1244, last paragraph of the Introduction, of Weil *et al.* (2002) *BioTechniques* 33:1244-1248).

These references indicate that, not only is the transfection of cells with siRNA different than transfection of cells with DNA, but siRNA transfection is complicated and the transfection procedure varies significantly from cell-type to cell-type. In summary, Applicants respectfully submit that the ordinarily skilled artisan at the time of Applicants' invention would not have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) in view of Clancy *et al.* (US 20030087259).

Finally, Applicants respectfully submit that the ordinary artisan would not have been motivated to combine the teachings of the Al-Hasani *et al.* with those of Clancy *et al.* to arrive at Applicants claimed methodology. Even if the skilled artisan were to rely on Clancy *et al.* for teaching that siRNAs as an agent capable of blocking gene expression, he would not have been motivated to substitute the ***DNA plasmids*** transfected in Al-Hasani with such siRNAs. The mere fact that Clancy *et al.* lists siRNAs and dominant negative mutants as potential gene blocking compounds in a more extensive list of gene blocking compounds, *e.g.*, antisense molecules, ribozymes, triplexes, aptamers, does not arise to the level of a motivation to select one specific member from the recited antagonist list for use in the featured methodology. Moreover, there is nothing in Clancy et al. which would motivate a skilled artisan to combine the teachings with those of Al-Hasani *et al.* to arrive at the claimed methods for identifying

[3] A copy of which is attached herein as Appendix F.
[4] A copy of which is attached herein as Appendix G.

genes affecting glucose transport or genes involved in insulin-response diseases or disorders. In particular, Clancy relates to diagnostic and therapeutic methods for detecting and/or treating bone and cartilage formation and is wholly unrelated to the art of glucose transport.

The Office Action has failed to point to any teaching in the cited references which would impel one of ordinary skill in the art to combine the teachings of the references in order to arrive at the presently claimed invention. It is well-established law that the prior art must suggest "to those of ordinary skill in the art that they ***should*** make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success ***must be founded in the prior art, not in the applicant's disclosure*** (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988). Thus, absent evidence to the contrary, the combination of the two cited references amounts to an attempt at hindsight reconstruction of the claimed invention based on the teachings of Applicants' own specification and is clearly impermissible. See, for example, *In re Fine* 5 USPQ2d 1596 (Fed.Cir. 1988); *In re Gorman* 18 USPQ2d 1885 (Fed. Cir. 1991); *In re Fitch* 23 USPQ2d 1780 (Fed. Cir. 1990).

In summary, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) in view of Clancy *et al.* (US 20030087259). For the foregoing reasons, rejection of the claimed invention is believed to be improper and Applicants respectfully request that it be reconsidered and withdrawn.

Rejection of claims 38-43, 84, and 85 under 35 U.S.C. § 103(a)

The Examiner has rejected claims 38-43, 84, and 85 as being unpatentable over Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of Paquerequ *et al.* (Anal. Biochem. 204(1):147-151, 1992). The Examiner's comments with respect to Al-Hasani and Clancy are summarized above. The Office Action states that "Paquereau taught a method of delivering nucleic acids to mammalian cells by electroporation using a potential of 0.15-0.2kV and a capacitance of 960 micro F." In summary, the Office Action states that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the electrical potential and capacitance used in the

electroporation of the cells of Al-Hasani because it was recognized in the art that these variables could affect the amount of cell damage caused by electroporation, as well as cellular survival after electroporation."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

The currently pending claims are set forth as above. To briefly summarize, the amended claims are directed to a method of identifying a gene in adipocytes that affects glucose transport or a gene involved in an insulin response disease or disorder, and that it is essential to the method that electroporation of siRNA into a culture of adipocytes be ***efficient*** and that ***the adipocyte population exhibit sufficient reduction in expression of the targeted gene to be able to reliably assay that gene's effect on glucose transport***.

The legal requirements to establish a *prima facie* case of obviousness are also set forth above. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness since at the time the invention was made there was no motivation to combine the references in the manner suggested by the Examiner, nor was there a reasonable expectation of success in making the claimed invention. The teachings of Al-Hasani *et al.* and Clancy *et al.* are set forth above. As discussed previously, based on the teachings of the references, there was no reasonable expectation of success in making the claimed invention. Additionally, the Examiner has not provided the requisite motivation to combine these references.

The Paquereau reference does not teach or suggest the claimed invention either alone or in combination with the Al-Hasani and Clancy references. Paquereau describes the transfection of ***hepatocyte cells with DNA*** (see e.g., page 148, column 2, lines 1-4 of Paquereau *et al.*). In particular, Paquereau describes the electroporation of high concentrations of isolated hepatocytes (*e.g.*, 16-20 x 10^6 heaptocytes, *i.e.*, 20-25 x 10^6 hepatocytes per 0.8 ml) with large amounts of plasmid DNA (*e.g.*, 30 μg DNA per 0.8ml) in the presence of large amounts of carrier DNA (*e.g.*, 400 um). The transfection methods are optimized to obtain high levels of expression of the reporter gene CAT. As discussed previously, siRNAs and plasmid DNA are quite different chemical entities. Accordingly, one of skill in the art at the time of the instant invention would not have not had a reasonable expectation of success in utilizing certain of the parameters disclosed in Paquereau for transfection of large amounts of plasmid DNA to arrive at the siRNA electroporation methods featured in the claimed invention based upon this teaching, nor would

one be motivated to combine these references. Moreover, there is nothing in Paquereau *et al.* which would motivate a skilled artisan to combine the teachings with those of Al-Hasani *et al.* and Clancy *et al.* to arrive at the claimed methods for identifying genes affecting glucose transport or genes involved in insulin-response diseases or disorders. Paquereau *et al.* relates to DNA transfection of hepatocytes to preserve a growth hormone response and is wholly unrelated to the art of glucose transport.

In view of the foregoing, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of Paquerequ *et al.* (Anal. Biochem. 204(1):147-151, 1992). Therefore, the claimed invention is not obvious in view of the cited art. Applicants respectfully request withdrawal of the rejection of claims 38-43, 84, and 85 under 35 U.S.C. §103(a) and favorable reconsideration.

Rejection of claim 49 under 35 U.S.C. § 103(a)

The Examiner has rejected claim 49 as being unpatentable over Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of Standaert *et al.* (J. Biol. Chem. 272(48):30075-30082, 1997). The Examiner's comments with respect to Al-Hasani and Clancy are summarized above. The Examiner states that, "Standaert taught methods of studying the effect of a gene expression of protein kinase C zeta (PKC-zeta) on glucose transport." The Office Action summarizes that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to extend the studies of Al-Hasani to studies of glucose uptake."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

The currently pending claims are set forth as above. To briefly summarize, the amended claims are directed to a method of identifying a gene in adipocytes that affects glucose transport or a gene involved in an insulin response disease or disorder, and that it is essential to the method that electroporation of siRNA into a culture of adipocytes be ***efficient*** and that ***the adipocyte population exhibit sufficient reduction in expression of the targeted gene to be able***

to reliably assay that gene's effect on glucose transport. The legal requirements to establish a *prima facie* case of obviousness are set forth above. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness since at the time the invention was made there was no motivation to combine the references in the manner suggested by the Examiner, nor was there a reasonable expectation of success in making the claimed invention. The teachings of Al-Hasani *et al.* and Clancy *et al.* are set forth above. As discussed previously, based on the teachings of the references, there was no reasonable expectation of success in making the claimed invention. Additionally, the Examiner has not provided the requisite motivation to combine these references.

The Standaert reference does not teach or suggest the claimed invention either alone or in combination with the Al-Hasani and Clancy references. Standaert, like Al-Hasani, is directed toward the study of insulin stimulation in glucose transport by transfection of ***rat adipocytes with plasmid DNA*** (see *e.g.*, page 148, column 2, lines 1-4 of Standaert *et al.*). Like Al-Hasani, Standaert fails to rectify the deficiency of teaching of features necessary to electroporation of siRNAs as in the claimed invention. Applicants submit that one of skill in the art at the time of the instant invention would not have not had a reasonable expectation of success in making the claimed invention based upon this teaching, nor would one be motivated to combine these references.

In view of the foregoing, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of Standaert *et al.* (J. Biol. Chem. 272(48):30075-30082, 1997). Therefore, the claimed invention is not obvious in view of the cited art. Applicants respectfully request withdrawal of the rejection of claim 49 under 35 U.S.C. §103(a) and favorable reconsideration.

Rejection of claims 52-55 under 35 U.S.C. § 103(a)

The Examiner has rejected claims 52-55 as being unpatentable over Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of McSwiggen *et al.* (US Patent 7,022,828). The Examiner states on page 10 of the Office Action that, "[t]he teachings of Al-Hasani and Clancy... can be combined to render obvious

methods of identifying a gene that affects glucose transport by assaying insulin-mediated GLUT4 translocation in the presence or absence of dynamin, wherein dynamin concentration is modulated through siRNA delivered by electroporation." Further, on page 11, the Office Action states that "McSwiggen taught methods of inhibiting gene expression using siRNA, and taught that the stability of siRNA molecules could be enhanced through the use of modified bases." In conclusion, the Office Action summarizes that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to use modified siRNA oligonucleotides in the invention of Al-Hasani as modified by Clancy... in order to enhance the function of the oligonucleotides, as taught by McSwiggen."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

The McSwiggen reference does not teach or suggest the claimed invention either alone or in combination with the Al-Hasani and Clancy references. McSwiggen teaches modified siRNA oligonucleotides which modulate the expression or function of IKK genes, such as IKK-gamma, IKK-alpha, or IKK-beta, and PKR genes in several cell types. However, McSwiggen does disclose any details of transfecting ***adipocytes*** with siRNA. Thus, McSwiggen fails to rectify the deficiency of teaching of the Al-Hasani and Clancy references. Moreover, there is nothing in McSwiggen which would motivate a skilled artisan to combine the teachings with those of Al-Hasani *et al.* and Clancy *et al.* to arrive at the claimed methods for identifying genes affecting glucose transport or genes involved in insulin-response diseases or disorders. McSwiggen relates generically to the chemistry of siRNA derivatives and is wholly unrelated to the art of glucose transport.

In view of the foregoing, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of McSwiggen *et al.* (US Patent 7,022,828). Therefore, the claimed invention is not obvious in view of the cited art. Applicants respectfully request withdrawal of the rejection of claims 52-55 under 35 U.S.C. §103(a) and favorable reconsideration.

REMARKS

In view of the foregoing, entry of the amendments and remarks presented, favorable reconsideration and withdrawal of the rejections, and allowance of this application with the pending claim are respectfully requested. If a telephone conversation with the Applicant's attorney would expedite prosecution of the above-identified application, the Examiner is invited to call the undersigned at (617) 227-7400.

Dated: August 22, 2007

Respectfully submitted,

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